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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/135,238	08/17/98	NOLAN G	A-65635-1/DJ

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FLEHR HOHBACH TEST
ALBRITTON & HERBERT
4 EMBARCADERO CENTER SUITE 3400
SAN FRANCISCO CA 94111

EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	21

DATE MAILED: 08/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/135,238	Applicant(s) NOLAN ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-40 and 45-57* is/are pending in the application.

4a) Of the above claim(s) *41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-40 and 45-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Response filed 4-23-01 has been entered.

2. It is noted that in their response, Applicants have cancelled claims 1-34. However, claims 18-29, 31, and 33-34 were already cancelled in response to the amendment filed 9-30-99 (paper #9). Accordingly, only claims 1-17, 30, and 32 were pending at the time of the previous office action. Therefore, only claims 1-17, 30, and 32 have been cancelled in response to Applicants response and amendment of 4-23-01.

3. New claims 35-57 have been entered.

4. It is noted that claims are directed. Newly submitted claim 41-44 are directed to polypeptides, an invention that is independent or distinct from the invention originally claimed for the following reasons:

The chemical and physical properties, functions, utilities and methods of use of a protein are distinct compared to those of a nucleic acid. It is noted that Applicants have elected the invention of nucleic acids and the invention of proteins was withdrawn from further consideration (see the office action of 8-23-99, paper # 7).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 41-44 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. This application contains claims 41-44 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

6. Claims 35-40 and 45-57 are under consideration.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 35-40, 45-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 10-19-00 and as discussed below.

When the claims are analyzed in light of the specification, the genus of the instantly claimed invention would encompass, nucleic acids that hybridize to SEQ ID NO 1, or nucleic acids that have 90% sequence identity to SEQ ID NO 1 or that encode a protein that has 90% sequence identity to SEQ ID NO 2 or that encode a protein that would encode a protein comprising the amino acids 18-253 and 273-390 of SEQ ID NO 2 or that nucleic acids that encode proteins that have 90% sequence identity with amino acids 18-253 and 273-390 of SEQ ID NO 2, vectors comprising said nucleic acids, host cells that comprise said vectors and processes for producing proteins encoded by said nucleic acids expressed in host cells. It is noted that these nucleic acids would encompass both naturally occurring as well as synthetic allelic variants of SEQ ID NO 1 and isolated from different species including human. However, the specification discloses only Seq ID No 1 that encodes a polypeptide disclosed in SEQ ID NO 2. However, as noted in the previous office action, the specification discloses only one species of the claimed genus, SEQ ID NO 1 that encodes a TOSO polypeptide disclosed in SEQ ID NO 2. Since the claim does not recite the stringency of the hybridization condition, there would be substantial variation within genus because hybridization condition as broadly disclosed in the specification would be expected to yield structurally

unrelated nucleic acid molecules. The single disclosed species is not representative of the genus because there is no structural attribute or feature that is common to the members of the group.

Response to Arguments

Applicant's arguments filed 4-23-01 have been fully considered but they are not persuasive. In response to Applicants' arguments that SEQ ID NO 3-21 depict sequence alignment of nucleic acids identified by BLAST and are depicted in Figure 3, it is noted that figure 3 does not provide any description as to which sequence is SEQ ID NO 3 and which one is SEQ ID NO 21 etc. Furthermore, figure 3 has only 12 sequences whereas SEQ ID NO 3-21 are total 19 sequencS. It is not clear as to how an artisan can comprehend as to how 12 sequences of figure 3 represent 19 different sequences disclosed in SEQ ID NO 3-21.

Next Applicants have argued that the meaning of hybridization is generally described at page 13, line 22 and therefore the specification sufficiently describes SEQ ID NO 1 and 2. It is noted that the indicated section of specification on page 13 refers to molecular biology manuals for the definition of hybridization and gives 65 degree as an example, however, since the condition is not recited in the claim, it would encompass any hybridization condition contemplated by the disclosure. Therefore, there would be substantial variation within genus of the nucleic acids obtained because hybridization condition as broadly disclosed in the specification would be expected to yield structurally unrelated nucleic acid molecules. In other words, an artisan would not know whether the Applicants had the possessions of the claimed nucleic acids at the time of the invention. Applicants argue that they have described two deletion fragments, 18-253 and 273-390, which is one characteristic, however, these are not the representative of all the species encompassed by the claimed nucleic acid because the claimed invention encompasses any nucleic acid that hybridizes to these fragments and has 90% sequence identity and as discussed for SEQ ID NO 1 and 2, due to the lack of the hybridization conditions, an artisan would expect to see substantial variation within the genus of the nucleic acids. Again an artisan would not know whether Applicants

had possession of the vast genus of nucleic acids recited at the time of the invention. Applicants have cited parts of the written description guidelines and case laws re smith and re Lukach and argue that specification is required to contain a statement that adequately describes the invention as claimed. In response it is noted that mere statement is not sufficient to adequately describe an invention because description should be sufficient to indicate that the Applicants had the possession of the claimed invention at the time of the invention and as discussed above and in the previous office action, in the instant case, the specification does not provide sufficient description of the claimed invention to indicate that the Applicants had the possession of the claimed invention as the time of the invention.

9. Claims 35-40 and 45-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleic acid disclosed in SEQ ID NO 1 which encodes the protein disclosed in SEQ ID NO 2, a recombinant nucleic acid that encodes amino acids 18-253 or 273-390 of SEQ ID NO 2, an expression vector comprising said recombinant nucleic acids, a host cell comprising the expression vectors and a process of producing the protein encoded by the recombinant nucleic acids by culturing said host cells and recovering the proteins from said host cells, does not reasonably provide enablement for other embodiments claimed, for reasons of record set forth in the previous office action of 10-19-00. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As noted in the previous paragraph (#10), instantly presented claims encompass nucleic acids of SEQ ID NO 1, that encodes SEQ ID NO 2 and AA 18-253 or 273-390 of SEQ ID NO 2 and nucleic acids that have 90% sequence identity to SEQ ID NO 1, or encode a polypeptide that has 90% sequence identity to SEQ ID NO 2 and AA 18-253 or 273-390 of SEQ ID NO 2 and any naturally occurring or synthetic allelic variants . However, these amendments do not obviate the rejections set forth in the previous office action and the newly presented claims are

rejected for the reasons of record set forth in the previous office action of 10-19-00.

In view of the written description rejections discussed in paragraph 8, an artisan would not have been able to make and use the vast genus of nucleic acids encompassed by the claimed invention because the specification does not provide sufficient description of the structural and functional attributes of the representative species of the genus of nucleic acids encompassed by the claim invention

Furthermore, As noted in the previous office action of 10-19-00, it is noted that a recombinant nucleic acid that encodes a protein whose amino acid sequence differs by only one amino acid would hybridize to SEQ ID NO 1, however, such a mutant protein may not have the activity of TOSO protein. The issue is: would a representative number of polynucleotides as encompassed by claim 1 have the biological activity of a TOSO protein as claimed. For example, would a representative number of polynucleotides in which 10% of the nucleotide sequences are different compared to the sequence disclosed in SEQ ID NO 1 would encode a polypeptide that would have the biological activity and function of the wild type protein of SEQ ID NO 2. These proteins would include synthetic mutants and variants produced by deletion, substitution, and addition in the wild type polynucleotides such that up to 10% of nucleotides would be different from the sequence of SEQ ID NO 1. For example, it is noted that SEQ ID NO 1 contains 1910 nucleotides, which encodes for a protein of 390 amino acids. A change in 10% of this polynucleotide would be 191 nucleotides that would encode 63 amino acids. And this would correspond to a change in every other amino acid of the polypeptide encoded by SEQ ID NO 1. As noted in the previous office action (page 6), the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein. The specification does not teach which changes in the amino acid sequences of the SEQ ID NO 2 would retain the function of the protein of SEQ ID NO 2 or other polypeptides encompassed by the claimed invention and therefore, the nucleic acids encoding such amino acid

sequences could not be used for the intended utilities. The specification does not teach how to use a nucleic acid that would have encoded a protein which was derived from the protein of SEQ ID NO 2 but did not have the function of the starting protein. Alternatively, the specification does not teach how would an artisan have made a polynucleotide that would have encoded a protein in which 10% amino acids would have been changed but the protein would have retained the function of the starting protein.

Response to Arguments

Applicant's arguments filed 4-23-01 have been fully considered but they are not persuasive. It is noted that in the previous office action, specific issues based on sound scientific reasoning were raised, however, Applicants have not discussed/responded to these issues.

In conclusion, the specification as filed does not provide sufficient guidance, evidence, and working example, as to how an artisan of skill would have made and used the claimed invention commensurate in scope with claims and therefore, limiting the invention to a recombinant nucleic acid disclosed in SEQ ID NO 1 and which encodes the protein disclosed in SEQ ID NO 2, a recombinant nucleic acid that encodes amino acids 18-253 or 273-390 of SEQ ID NO 2, an expression vector comprising said recombinant nucleic acids, a host cell comprising the expression vectors and a process of producing the protein encoded by a recombinant nucleic acids by culturing said host cells and recovering the proteins from said host cells, is proper.

10. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing apoptosis in an isolated mammalian T cells or a method of increasing or decreasing apoptosis in a B cell in vitro comprising administering to said isolated mammalian T or B cells a recombinant expression vector wherein said recombinant expression vector expresses the protein disclosed in SEQ ID NO 2, does not reasonably provide enablement for a method of treatment of apoptosis related condition in a mammal

and other claimed embodiments, for reasons of record set forth in the previous office action of 10-19-00. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 57 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

Applicant's arguments filed 4-23-01 have been fully considered but they are not persuasive.

Regarding claim 56 (the activity of TOSO protein mediated modulation of apoptosis) Applicants have argued that TOSO mRNA was expressed in cell lines other than T cells. While the results of the Applicants regarding the expression pattern of TOSO mRNA are not contested, it is noted that the specification discloses on page 45, lines 19-22, "All of the human T cell lines and one of the human B cell lines, Oil-Ly8 cells in which TOSO was overexpressed, were inhibited for apoptosis induced by anti-Fas mAb, whereas no significant protection was observed against Fas-induced apoptosis in the other cell lines (data not shown)." This disclosure in the specification supports Examiner's position that TOSO does not inhibit apoptosis in all the cell lines or cell types. Additionally, the specification further indicates that TOSO induced apoptosis in 70z/3, pre-B cells but not in other cell lines (lines 25-27, page 49 of the specification).

Regarding claim 57, it is noted that Applicants have not discussed/responded to the scientific issues raised in the previous office action based on sound scientific reasoning and raised by experts in the field of gene therapy. Applicants have cited an article regarding gene therapy of cancer using p53. It is noted that although, specific vectors, promoters, genes, and routes of administration might be or may

have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect as discussed by various pre- and post-filing arts cited in the previous office action of 10-19-00. It is reiterated that numerous factors complicate the gene delivery art, which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient and the specification does not provide guidance and working examples as to how an artisan of skill would have had addressed these art recognized limitations of the method of gene therapy and because these limitations would not have been overcome by routine experimentation, an artisan of skill would have required undue experimentation to practice the claimed invention.

In conclusion, the specification as filed is not enabling for in vivo method of inhibiting apoptosis in any cells or a method of treatment of apoptosis related conditions and an artisan would have required undue experimentation to make and use the invention commensurate in scope with the claims and therefore, limiting the scope of the invention to a method of modulating apoptosis in an isolated mammalian T or B cells in vitro comprising administering to said isolated mammalian hematopoietic cell a recombinant expression vector wherein said recombinant expression vector expresses the protein disclosed in SEQ ID NO 2, is proper.

11. Claims 45-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-48 are vague and indefinite because it recites the phrase ".....identity to the amino acid sequence set forth by amino acids...." It is unclear as to what would be considered "amino acid sequence set forth by amino acids" and the specification does not define the phrase.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is

(703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

14. Ram R. Shukla, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER